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PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Fumaramic Acid Derivatives

We UNIROYAL, INC. (formerly United States Rubber Company), of Rockefeller Centre, 1230 Avenue of the Americas, New York, State of New York, United States of America, a corporation organized and existing under the laws of the State of New Jersey, United States of America. do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

The present invention relates to new compounds and their method of preparation. More specifically, the invention describes N-[disubstituted amino] fumaramic acids and derivatives thereof. These compounds are useful as plant growth regulants and fungicides as is described and claimed in our copending Application No 36112/66 (Serial No. 1,117036).

The N-[disubstituted amino] radicals are dialkylamino, 1-pyrrolidyl, 1-piperidyl, or 4-morpholinyl; and one of the carbon atoms of the intermediate double-bonded carbon atoms of the fumaramic acid may carry a lower alkyl group. Additionally, salts and esters of the N-[disubstituted amino] fumaramic acids as well as salts of these esters with strong mineral acids are within the scope of the invention.

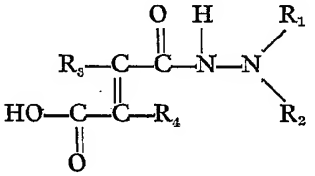
The N-[disubstituted amino] fumaramic acids are prepared by the isomerization of a strong acid salt of the corresponding N-[disubstituted amino] maleiamic acid. These latter compounds may be prepared as described in our Patents Nos. 954,102 and 1,014,912.

Included within the scope of the invention, in addition to the free acids, are their salts, such as the alkali salts, i.e., alkali metal, alkaline earth metal, ammonium or amine (substituted ammonium) salts, e.g., sodium, potassium, calcium, ammonium, methyl ammonium, dimethyl ammonium, trimethyl ammonium, ethyl ammonium, ethanol ammonium, diethanol ammonium, or triethanol ammonium salts. The salts may readily be formed directly from the acid and a selected base such as an alkalimetal hydroxide or carbonate, or ammonia, or an amine.

Additionally, by protonation of the disubstituted amino groups, salts of strong mineral acids may be formed. Such salts include for example the hydrohalide (e.g., hydrochloride), phosphate, and sulfate.

The esters of the N-disubstituted amino fumaramic acids, such as the alkyl esters having 1 to 12 carbon atoms in the esterifying radical, and the alkenyl esters having 3 to 4 carbon atoms in the esterifying radical may be used as plant growth regulants, e.g., the methyl, ethyl, propyl, butyl, octyl, dodecyl, allyl and methallyl esters. The esters may be formed by esterifying the selected N-[disubstituted amino] fumaramic acid with the selected alcohol, or directly from the maleamic acid or maleimide component by performing the isomerizaztion in an alcoholic medium. Also the salts of these esters with strong mineral acids have been prepared.

The preferred N-[disubstituted amino] fumaramic acids of the present invention are those represented by the general formula:



wherein R_1 and R_2 each stand for an alkyl group having 1 to 12 carbon atoms or R_1 and R_2 compositely stand for a $-(CH_2)_4-$, $-(CH_2)_5-$ or $(-CH_2CH_2)_2O$ group; and R_3 and R_4 each stand for hydrogen, or one of R_3 and R_4 stands for hydrogen and the other

[*Price 4s. 6d.*]

stands for a lower alkyl group having 1 to 8 carbon atoms, e.g. methyl, butyl, octyl.

Examples of chemicals of the present invention are:

N-[Dimethylamino] fumaramic acid
N-[Dimethylamino] fumaramic acid hydrochloride
N-[Dimethylamino] fumaramic acid phosphate
N-[Dioctylamino] fumaramic acid
N-[Didodecylamino] fumaramic acid
N-(4-morpholinyl) fumaramic acid
N-(1-piperidyl) fumaramic acid
N-(1-pyrrolidyl) fumaramic acid
Sodium N-(dimethylamino) fumaramate
Calcium N-[dimethylamino] fumaramate
Isopropyl N-[dimethylamino] fumaramate
Ethyl N-[dimethylamine] fumaramate hydrochloride
N-[dimethylamino] mesaconamic acid
Ethyl N-[dimethylamino] fumaramate
Diethanolammonium salt of N-[dimethylamino] fumaramic acid
Allyl N-[dimethylamino] fumaramate
Methallyl N-[dimethylamino] fumaramate hydrochloride

It is well known that maleic acid and many of its simple derivatives can be rearranged to the fumaric form by heating with catalytic amounts of halogens, halogen acids, Lewis acids ($AlCl_3$, $ZnCl_2$, $FeCl_3$,), sulfur and sulfur halides, as well as by catalytic surfaces in noble metal catalysts. By using these known methods in several attempts to effect the desired *cis*- to *trans*-rearrangement in the case of N-dimethylaminomaleamic acid, no rearrangement was achieved. The use of 1% by weight of iodine in refluxing acetonitrile resulted only in the recovery of unchanged starting material. Replacement of the iodine by sulfur in a similar procedure resulted in extensive decomposition and resinification. No rearrangement was achieved when N-dimethylaminomaleamic acid was refluxed in acetonitrile in the presence of 6% by weight of 5% palladium on carbon catalyst. The use of concentrated aqueous hydrochloric acid resulted in extensive hydrolysis and the formation of fumaric acid.

In accordance with invention, it has been discovered that the N-[disubstituted amino] fumaramic compounds of the present invention may be prepared by the rearrangement of the N-[disubstituted amino] maleamic compounds, wherein the latter disubstituted amino group has been protonated (has an H^+ ion). The isomerization reaction must be carried out in an inert reaction medium. The protonated maleamic form may then be rearranged with a conventional maleic acid isomerization catalysts.

The protonation of the disubstituted amino group of the maleamic form may be readily achieved by forming an acid salt with strong acids which do not cause adverse side effects such as oxidation, dehydration, or hydrolysis. The hydrogen halide salts are the most preferable reactants, particularly the hydrogen chloride and the hydrogen bromide.

Inert reaction media include any liquid which will not hydrolyze, oxidize, or dehydrate the reactants. Examples of these are the carboxylic acids, carboxylic acid nitriles and the halosubstituted carboxylic acids, such as glacial acetic acid and propionic acid, and acetonitrile. Various other solvents can be used depending on the physical properties of the particular substituted amino maleamic derivative to be rearranged. The best results, however, are obtained with glacial acetic acid and acetonitrile.

If the desired products are the esters of the N-[-disubstituted amino] fumaramic acid, the appropriate alcohol can be used as the reaction medium. It is thus possible to effect both esterification of the N-[disubstituted amino] maleamic acid (or its imide) and the rearrangement of the fumaramic ester all in one step. Though, in this case the solvent is not, strictly speaking, inert, it does permit the formation of the basic fumaramic structure.

The isomerization of the maleamic form to the fumaramic form is conveniently carried out in the presence of non-oxidizing maleic acid isomerization catalysts in order to minimize undesired side reaction. Catalysts which may conveniently be used include hydrohalic acids, iodine, and aluminium chloride.

The catalytic isomerization is carried out at a temperature of from 20 to 120° C. preferably from 75° to 85° C, in the presence of 0.02 to 20% of catalyst, preferably 0.1 to 10% by weight.

The following examples serve to more specifically illustrate the present invention:

EXAMPLE I

Preparation of N-[dimethylamino] fumaramic Acid

When a partial solution of 15.8 g. (.10 mole) of N-[dimethylamino] maleamic acid (m.p. 124—125°) in 40 g. of glacial acetic acid was treated with anhydrous HCl until 4.0 g. (.11 mole) had been absorbed, there resulted complete solution of all the solid in the warm solution. The molar excess of the HCl served as the catalyst. After heating to 75—80° C. on a steam plate for 1/2 hr. a solid crystalline mass had formed. This mixture was then allowed to cool to room temperature over 1 hour and then treated with 30 g. of acetonitrile. The cake was broken and the resulting slurry cooled in an ice bath fo 1/2 hr. Filtration and washing with 50 g. of cold acetonitrile gave 17 g. (90% yield) of N-[dimethylamino] fumaramic acid hydrochloride

as colorless crystals of m.p. 213—215° C. (d).

Neutral equivalent	Calc'd. 97
	Found 97

This product readily dissolves in water to give a strongly acidic (pH 1—2) solution. When a solution of 5 g. of this product in 10 ml. of water was treated with concentrated aqueous NH_3 until the pH of the solution had been raised to 4—5, there resulted the precipitation of N-[dimethylamino] fumaramic acid as a white solid. Filtration and washing with cold water gave 4.0 g. of colorless crystals of m.p. 214—216° C. (d).

Example II

To a partial solution of 15.8 g. (.10 mole) of N-[dimethylamino] maleamic acid (m.p. 124—125°) in 50 g. of glacial acetic acid was added anhydrous HCl until 3.6 g. (.10 mole) had been absorbed. After adding .05 g. of iodine crystals, the resulting yellow solution was heated on a steam plate to 70—80° C. for 2-1/2 hrs. and then allowed to cool to room temperature over 2 hrs. Filtration, followed by washing with ether, gave 14 g. of N-[dimethylamino] fumaramic acid hydrochloride as colorless crystals of m.p. 214—216° C. (d).

Example III

To a suspension of 15.8 g. (.10 mole) of N-[dimethylamino] maleamic acid (m.p. 124—125° C.) in 35 g. of glacial acetic acid was added 3.6 g. (.10 mole) of anhydrous HCl. To the resulting clear solution was added 0.10 g. of anhydrous $AlCl_3$. Within 5 minutes after placing on the steam plate the contents of the flask set to a solid mass of white crystals. After allowing to stand at room temperature for 1 hour the cake was broken and 30 g. of acetonitrile was added. Filtration, followed by washing with acetonitrile, gave 16 g. of N-[dimethylamino] fumaramic acid hydrochloride of m.p. 213—215° C. (d).

These three examples show that in practicing this new process it is essential to completely neutralize the hydrazine moiety as the salt of a strong mineral acid and that the *cis* to *trans* rearrangement can subsequently be catalyzed by small amounts of non-oxidizing maleic acid isomerization catalysts such as iodine, $AlCl_3$ and hydrogen halide.

Esters of N-[dimethylamino] fumaramic acid are readily prepared by refluxing the hydrochloride salt with the appropriate alcohol to yield the ester hydrochloride from which the free ester can be liberted by the addition of base to an aqueous solution of the ester hydrochloride. In this manner the following esters were prepared:

Methyl - N - [dimethylamino] fumaramate hydrochloride, m.p. 132—134° C.

Methyl - N - [dimethylamino] fumaramate, m.p. 141—143° C.

Ethyl - N - [dimethylamino] fumaramate hydrochloride, m.p. 119—122° C.

Ethyl - N - [dimethylamino] fumaramate, m.p. 134—136° C.

Example IV

Preparation of N-(1-piperidyl) fumaramic acid

To a mixture of 12 g. of N-(1-piperidyl) maleamic acid hydrochloride [m.p. 153—156° C. (d)] and 40 g. of glacial acetic acid was added 0.10 g. of $AlCl_3$. When heated to 70—75° C. for 1 hour, the solid initially present soon dissolved completely and then a new solid gradually precipitated. After adding 20 g. of acetonitrile and cooling in an ice bath for 1/2 hour, filtration gave 7.0 g. of N-(1-piperidyl) fumaramic acid hydrochloride as colorless crystals of m.p. 216—218° C. (d).

To a solution of 5 g. of this product in 15 ml. of water there are gradually added sufficient aqueous ammonia to raise to the pH to 4—5. The solid which precipitated was collected by filtration and washed with cold water. There was obtained 4.0 g. of N-(1-piperidyl) fumaramic acid as colorless crystals of m.p. 215—207° C. (d).

Example V

Preparation of N-[dimethylamino] mesaconamic acid hydrochloride

To a partial solution of 5.0 g. (.03 mole) of N-[dimethylamino] citraconamic acid (m.p. 123—125°) in 15 g of glacial acetic acid was added 2.0 g. (.005 mole) of anhydrous HCl. As the introduction of the HCl was completed, all of the solid dissolved in the warm solution and then suddenly a new precipitate formed rapidly. After allowing to stand for 20 minutes, 15 g. of acetonitrile was added and the mixture cooled in an ice bath for 1/2 hour. Filtration yielded 3.0 g. of N-[dimethylamino] mesaconamic acid hydrochloride as colorless crystals of m.p. 140—142° C.

Example VI

Preparation of N-(4-morpholinyl) fumaramic acid

When a mixture of 10 g. (.05 mole) of N-(4-morpholinyl) maleamic acid (m.p. 172—174° C.) and 80 g. of glacial acetic acid was heated to 70° C., complete solution of the solid resulted. Into this hot solution was passed anhydrous HCl until 3.6 g. (.10 mole) had been absorbed. This resulted in a rise in temperature of the mixture to 80° C. and the precipitation of a small amount of the hydrochloride salt. Heating to 85—88° C. caused complete solution of all solids. At this point 0.2 g. of $AlCl_3$ was added. This caused the rapid formation of a precipitate. After continuing heating to 80—85° C. for 15 minutes, this mixture was allowed to cool to room temperature over 1/2 hour. Sub-

sequent cooling in an ice bath, followed by filtration and washing with ether, gave 10 g. of N-4-morpholinyl) fumaramic acid hydrochloride as colorless crystals of m.p. 204—206° C. (d). This product, upon treatment with water, readily hydrolyzes to HCl and N-(4-morpholinyl) fumaramic acid which precipitates as colorless crystals of m.p. 221—224° C. (d).

Example VII

This example demonstrates that N-(dimethylamino) fumaramic acid hydrochloride can be prepared in one operation from maleic anhydride, 1,1-dimethylhydrazine and anhydrous HCl without isolating the intermediate N-(dimethylamino) maleamic acid.

To a solution of 49 g. (.50 mole) of maleic anhydride in 100 g. of glacial acetic acid was gradually added a mixture of 30 g. (.50 mole) of 1,1-dimethylhydrazine and 75 g. of glacial acetic acid. This latter mixture was prepared by the gradual addition, with cooling, of the 1,1-dimethylhydrazine to the acetic acid.

While adding this mixture to the solution of maleic anhydride in acetic acid, cooling was employed so that the temperature of the reaction mixture did not exceed 30° C. The resulting clear yellow solution was allowed to stand at room temperature for 15 minutes.

When 19 g. (.52 mole) of anhydrous HCl was passed into this solution, the temperature rapidly rose to 70—75° C. After standing for 1/2 hour the original pale yellow solution had set to a solid mass of white crystals. After standing for an additional 1 hour, 100 ml. of acetonitrile was added and the resulting slurry filtered. The filter cake was washed with 50 ml. of acetonitrile then with two 100 ml. portions of ether. There was obtained 70 g. of N-(dimethylamino) fumaramic acid hydrochloride as colorless crystals of m.p. 212—215° C. (d).

Example VIII

The rearrangement may be carried out in acetonitrile in a manner similar to that using acetic acid. To a suspension of 7.9 g. (0.05 mole) of N-dimethylaminomaleamic acid in 20 ml. of acetonitrile was added 2.0 g. (0.055 mole) of hydrogen chloride. The mixture became warm and the solid dissolved. Warming the solution on a steam bath resulted in some precipitate formation within 5 minutes. Precipitate formation was complete in 15 minutes. After adding 20 ml of ether, filtration of the slurry yielded 9.5 g. (98% yield) of N-dimethylaminofumaramic acid hydrochloride identified by its infrared spectrum.

Example IX

To a suspension of 31.0 g. (0.2 mole) of N-dimethylaminomaleamic acid in 100 ml. of methanol was added 8.0 g. (0.22 mole) of hydrogen chloride. Solution of the solid occurred upon heating to reflux. After 15 hours of refluxing the methanol was removed having a yellow, oily residue. This was dissolved in water and the solution then made slightly basic by the addition of dilute ammonia. The resultant precipitate was filtered and identified as methyl-N-dimethylaminofumaramate m.p. 141—3° C. and by its infrared spectrum.

Example X

The isomerization and esterificcation are carried out in one step in this example as follows:

To a solution of 11.5 g. (0.082 mole) of N-dimethylaminomaleimide in 50 ml. of ethanol was added 3.2 g. (0.088 mole) of hydrogen chloride. The solution was refluxed for 1-1/2 hours and then concentrated by removal of the methanol under reduced pressure. The addition of ether caused the precipitation of an oil which crystallized. There was obtained 15 g. (83% yield) of ethyl-N-dimethylaminofumaramate hydrochloride identified by its infared spectrum.

Example XI

A suspension of 1.6 g. (0.01 mole) of N-dimethylaminomaleamic acid in 25 ml. of acetonitrile was treated with 0.015—0.020 mole of anhydrous hydrogen bromide. Upon initial warming on a steam bath solution occurred. After a few minutes there was precipitated a solid of m.p. 187—190° C. Conversion of the salt to the free base yielded N-dimethylaminofumaramic acid m.p. 213—215° C. (d).

WHAT WE CLAIM IS:—

1. An N-(dialkylamino), N-(1-pyrrolidyl), N-(1-piperidyl) or N-(4-morpholinyl) derivative of fumaramic acid or of a C-alkyl fumaramic acid, or an acid or base salt, or an ester, or a salt of an ester of said derivative.
2. A compound as claimed in Claim 1, which is an N-(dimethylamino) derivative.
3. A compound as claimed in Claims 1 or 2 which is a methyl ester or a hydrochloride salt.
4. A compound as claimed in Claims 1 or 2 which is N-(dimethylamino) fumaramic acid.
5. A compound as claimed in Claims 1 or 2 which is N-(dimethylamino) fumaramic acid hydrochloride.
6. A compound as claimed in Claims 1 or 2 which is N-(dimethylamino) fumaramic acid phosphate.
7. A compound as claimed in Claim 1 which is N-(dioctylamino) fumaramic acid.
8. A compound as claimed in Claim 1 which is N-(didodecylamino) fumaramic acid.
9. A compound as claimed in Claim 1 which is N-(4-morpholinyl) fumaramic acid.

10. A compound as claimed in Claim 1 which is N-(1-piperidyl) fumaramic acid.

11. A compound as claimed in Claim 1 which is N-(1-pyrrolidyl) fumaramic acid.

12. A compound as claimed in Claims 1 or 2 which is Sodium N-(diethylamino) fumaramate.

13. A compound as claimed in Claims 1 or 2 which is Calcium N-(dimethylamino) fumaramate.

14. A compound as claimed in Claims 1 or 2 which is Isopropyl N-(dimethylamino) fumaramate.

15. A compound as claimed in claims 1 or 2 which is Ethyl N-(dimethylamino) fumaramate hydrochloride.

16. A compound as claimed in Claims 1 or 2 which is N-dimethylamino) mesaconamic acid.

17. A compound as claimed in Claims 1 or 2 which is Ethyl N-(dimethylamino) fumaramate.

18. A compound as claimed in Claims 1 or 2 which is Diethanolammonium salt of N-(dimethylamino) fumaramic acid.

19. A compound as claimed in Claims 1 or 2 which is Allyl N-(dimethylamino) fumaramate.

20. A compound as claimed in claims 1 or 2 which is Methallyl N-(dimethylamino) fumaramate hydrochloride.

21. A compound as claimed in Claim 1, substantially as described in the foregoing examples.

22. A method of making a compound as claimed in any one of Claims 1 to 20 which comprises protonating the corresponding N-(disubstituted amino)-derivative of maleamic acid or the corresponding C-alkyl maleamic acid and isomerising the protonated maleamic acid derivative with a maleic acid isomerisation catalyst in an inert reaction medium.

23. A method as claimed in Claim 22, wherein protonation of the maleamic acid derivative is effected using a hydrohalic acid.

24. A method as claimed in Claim 23 wherein the hyrohalic acid is hydrochloric acid.

25. A method as claimed in any one of claims 22 to 24 wherein the reaction medium is a carboxylic acid or a carboxylic acid nitrile.

26. A method as claimed in Claim 25, wherein the reaction medium is glacial acetic acid.

27. A method as claimed in any one of Claims 22 to 24, wherein the reaction medium is an alcohol, the ester of the fumaramic acid derivative being formed.

28. A method as claimed in any one of Claims 22 to 27 which is effected at a temperature of from 20 to 120° C.

29. A method as claimed in any one of claims 22 to 29 wherein the amount of catalyst is from 0.02 to 20% by weight.

30. A method as claimed in any one of claims 22 to 29 wherein the catalyst is a halogen, a halogen acid, a Lewis acid, sulphur, or a sulphur halide, or a noble metal.

31. A method as claimed in Claim 30, wherein the catalyst is a hydrohalic acid, iodine or aluminium trichloride.

32. A method as claimed in Claim 22, substantially as described in the foregoing examples.

33. A compound as claimed in any one of claims 1 to 20 when made by a method as claimed in any one of claims 22 to 32.

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